

Facile Large-Scale Synthesis of Coniferyl, Sinapyl, and *p*-Coumaryl Alcohol

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Coniferyl, sinapyl, and *p*-coumaryl alcohols are rapidly and cleanly prepared by selective 1,2-reduction of the corresponding cinnamate esters using diisobutylaluminum hydride (DIBAL-H) in toluene as reducing agent.

INTRODUCTION

Lignin biosynthesis is initiated by an enzyme-catalyzed phenol dehydrogenation of mixtures of *p*-hydroxy-*trans*-cinnamyl alcohol monomers, namely coniferyl (**2a**), sinapyl (**2b**), and *p*-coumaryl (**2c**) alcohols. A copolymerization follows during which resonance-stabilized phenoxy radicals produced from monomers and from the growing polymer couple in a variety of ways to build up the lignin macromolecule (Sarkanen, 1971; Harkin, 1967, 1973; Adler, 1977).

Lignin-like dehydrogenation polymers (DHPs) can be made *in vitro*, using mushroom laccase or horseradish peroxidase preparations (Freudenberg, 1956, 1968; Higuchi, 1971; Brunow and Wallin, 1981). Although synthetic dehydrogenative polymerization is a simplification of the lignification processes, it constitutes a unique tool to elucidate the lignin structural patterns and to study the possible chemical pathways followed during lignin biogenesis (Ralph et al., 1992; Higuchi, 1980) and degradation (Kirk et al., 1975; Kern et al., 1985; Faix et al., 1985; Kondo et al., 1990). However, such investigations have always been made difficult by the poor accessibility of the *p*-hydroxycinnamyl alcohols.

In the past, lithium aluminum hydride reduction of ethyl ferulate (**1a**) was the most commonly used synthetic route toward coniferyl alcohol (**2a**) (Allen and Byers, 1949; Freudenberg and Hübner, 1952; Freudenberg and Swaleh, 1969). Sodium bis(2-methoxyethyl)aluminum hydride was later used as reductant to obtain better 1,2-selectivity in the reduction of the conjugated ester **1a** (Minami et al., 1974; Kirk and Brunow, 1988). In both cases, varying amounts of saturated alcohol were observed due to competing 1,4- vs 1,2-attack by hydride. Newman et al. (1986) used the "ate" complex generated from diisobutylaluminum hydride and *n*-butyllithium (Kim and Ahn, 1984) to achieve the desired chemoselective reduction of **1a** in 64% yield. Over the years, different synthetic routes leading to *p*-hydroxycinnamyl alcohols have been reported, but all demand several steps and/or give only moderate overall yields (Nakamura and Higuchi, 1976; Steglich and Zechlin, 1978; Zanarotti, 1982). Finally, Rothen and Schlosser (1991) have synthesized coniferyl alcohol (**2a**) by metallation of eugenol with *n*-butyllithium/potassium *tert*-butoxide followed by dimethoxyborylation-oxidation in 81% yield, but the procedure is more demanding than are reduction methods.

We now report that simple DIBAL-H reduction of ethyl ferulate (**1a**) rapidly and cleanly affords coniferyl alcohol

(**2a**) in good yield and allows large-scale preparation. The method works equally well for preparing sinapyl (**2b**) and *p*-coumaryl (**2c**) alcohols.

EXPERIMENTAL PROCEDURES

Melting points are uncorrected. NMR spectra were run in acetone-*d*₆ on a Bruker AMX-360 instrument, operating at 360.13 MHz ¹H (90.55 MHz ¹³C). The central solvent signal was used as internal reference (¹H, 2.04 ppm; ¹³C, 29.8 ppm). Unambiguous assignments were obtained from proton-detected C-H chemical shift correlation spectra run with Bruker's INVTBP pulse program (Bax and Subramanian, 1986). For coniferyl alcohol (**2a**), the oxygenated aromatic carbons C₃ and C₄ were unambiguously assigned from proton-detected long-range C-H chemical shift correlation spectra run with Bruker's INV4PLRND pulse program (Bax and Summers, 1986).

Coniferyl Alcohol (2a). Ethyl ferulate (**1a**) was prepared from ferulic acid (Sigma) by stirring overnight with EtOH/HCl, produced by adding 10 mL of acetyl chloride to 100 mL of ethanol (Fieser and Fieser, 1967), and crystallized from ethyl acetate/petroleum ether. **1a** (2.13 g, 9.58 mmol) in toluene (100 mL, freshly distilled), under nitrogen, was cooled in an ice-water bath, and diisobutylaluminum hydride (Aldrich, 27 mL of 1.5 M solution, 40.5 mmol, 4.2 equiv) in toluene was slowly added via syringe over ca. 10 min. After addition was complete, stirring was continued for ca. 1 h. The reaction mixture was then carefully quenched with ethanol (5–10 mL). The solvents were partially removed *in vacuo* at 40 °C. Water (50 mL) was added, and the aqueous layer, containing a gelatinous precipitate of aluminum salts, was extensively extracted with ethyl acetate (4 × 150 mL). The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo* at 35 °C to give coniferyl alcohol (**2a**) generally as a white-pale yellow solid but sometimes as an oil (1.69 g, 98%). ¹H NMR of this crude **2a** showed only traces of 1,4-reduction products. Crystallization from dichloromethane/petroleum ether (bp 40–60 °C) gave **2a** as colorless plates (1.33 g, 77%): mp 77.9–78.6 °C (lit. 74–76 °C; Freudenberg and Hübner, 1952); ¹H NMR δ 3.78 (1 H, t, *J*_{OH-γ} = 5.65 Hz, OH), 3.85 (3 H, s, OCH₃), 4.18 (2 H, td, *J*_{γ-OH} ≈ *J*_{γβ} = 5.6 Hz, *J*_{γα} = 1.5 Hz, H_γs), 6.22 (1 H, dt, *J*_{βα} = 15.9 Hz, *J*_{βγ} = 5.5 Hz, H_β), 6.49 (1 H, dt, *J*_{αβ} = 15.9 Hz, *J*_{αγ} = 1.5 Hz, H_α), 6.76* (1 H, d, *J*₆₆ = 8.1 Hz, H₆), 6.84* (1 H, dd, *J*₆₅ = 8.1 Hz, *J*₆₂ = 1.9 Hz, H₆), 7.04 (1 H, d, *J*₂₆ = 1.9 Hz, H₂), 7.63 (1 H, s, Ar OH); ¹³C NMR δ (see Table I). (*ABq pattern, *J*_{AB} = 8.10 Hz, Δ_{AB} = 31.88 Hz.)

For large-scale preparation (10–20 g), the DIBAL-H solution in toluene was transferred to a dropping funnel via a double-tipped needle (Aldrich Technical Information Bulletin AL-134). Addition was accomplished dropwise over ca. 1 h. After quenching with ethanol, the precipitated aluminum salts were removed by filtration and thoroughly washed with ethyl acetate. The combined filtrate and washings were evaporated to dryness to

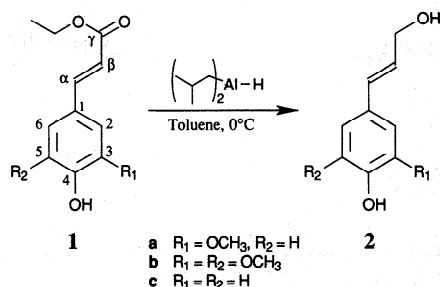


Figure 1. Reduction of ethyl cinnamates 1a–c by DIBAL-H in toluene to give hydroxycinnamyl alcohols 2a–c.

Table I. ^{13}C NMR Shifts of *p*-Hydroxy-*trans*-cinnamyl Alcohols (Solvent: Acetone- d_6)

	α	β	γ	OCH_3	1	2	3	4	5	6
2a	130.4	128.0	63.4	56.1	130.2	109.9	148.4	147.1	115.7	120.6
2b	130.6	128.3	63.3	56.5	129.0	104.6	148.7	136.5	148.7	104.6
2c	130.1	127.7	63.4		129.7	128.3	116.1	157.8	116.1	128.3

yield crude 2a. Crystallization from methylene chloride/petroleum ether afforded pure 2a in 65–70% yield.

Sinapyl Alcohol (2b). Ethyl sinapate (1b) was reduced as described for 1a to yield crude sinapyl alcohol (2b) as an oil. Crystallization from methylene chloride/petroleum ether gave pure 2b as white–yellow needles, in 70% yield: mp 66.5–67.3 °C (lit. 63–65 °C; Freudenberg and Dillenburg, 1951); ^1H NMR δ 3.88 (1 H, t, $J_{\gamma\text{OH}-\gamma} = 5.65$ Hz, OH_γ), 3.82 (6 H, s, OCH_3), 4.20 (2 H, td, $J_{\gamma-\text{OH}} \approx J_{\gamma\beta} = 5.6$ Hz, $J_{\gamma\alpha} = 1.5$ Hz, $\text{H}_{\gamma\text{s}}$), 6.24 (1 H, dt, $J_{\beta\alpha} = 15.8$ Hz, $J_{\beta\gamma} = 5.5$ Hz, H_β), 6.48 (1 H, dt, $J_{\alpha\beta} = 15.8$ Hz, $J_{\alpha\gamma} = 1.5$ Hz, H_α), 6.71 (2 H, s, H_2/H_6), 7.30 (1 H, s, Ar OH); ^{13}C NMR δ (see Table I).

***p*-Coumaryl Alcohol (2c).** Ethyl *p*-coumarate (1c) was reduced as described for 1a to yield crude *p*-coumaryl alcohol (2c) as a white–pale yellow solid. Crystallization from acetone/petroleum ether gave pure 2c as white fine crystals, in 92% yield: mp 89.3–90.5 °C; ^1H NMR δ 3.85 (1 H, t, $J_{\gamma\text{OH}-\gamma} = 5.65$ Hz, OH_γ), 4.19 (2 H, td, $J_{\gamma-\text{OH}} \approx J_{\gamma\beta} = 5.6$ Hz, $J_{\gamma\alpha} = 1.6$ Hz, $\text{H}_{\gamma\text{s}}$), 6.19 (1 H, dt, $J_{\beta\alpha} = 15.9$ Hz, $J_{\beta\gamma} = 5.6$ Hz, H_β), 6.50 (1 H, dt, $J_{\alpha\beta} = 15.9$ Hz, $J_{\alpha\gamma} = 1.6$ Hz, H_α), 6.78 (2 H, m, H_3/H_5), 7.25 (2 H, m, H_2/H_6), 8.40 (1 H, s, Ar OH); ^{13}C NMR δ (see Table I).

RESULTS AND DISCUSSION

Diisobutylaluminum hydride (DIBAL-H) is well-known as one of the most versatile reducing agents used in organic synthesis because of its ability to achieve stereo- and chemoselective reductions, particularly in the case of unsaturated carbonyl compounds (Winterfeldt, 1975). Thus, coniferyl (2a), sinapyl (2b), and *p*-coumaryl (2c) alcohols were obtained from their corresponding ethyl cinnamate derivatives (1a–c) via DIBAL-H reduction in toluene at 0 °C, in 77%, 70%, and 92% yield, respectively, as described under Experimental Procedures. The alcohols were characterized by ^1H and ^{13}C NMR spectroscopy (Table I; Experimental Procedures). Unambiguous spectral assignments were made using short- and long-range C–H chemical shift correlation experiments. We have concluded that the use of the “ate” complex from DIBAL-H and *n*-BuLi (Newman et al., 1986; Kim and Ahn, 1984) is unnecessary, since it affords no improvement in achieving 1,2-selectivity in these reductions. In addition, large-scale preparation can be easily accomplished with similar results by using a slightly modified procedure (see Experimental Procedures). Furthermore, the preparation of labeled *p*-hydroxycinnamyl alcohols is considerably easier than that by the Rothen and Schlosser method, since the ethyl cinnamate derivatives (1a–c) can be readily prepared with ^{13}C (or ^{14}C) labeling at any side-chain position (Newman et al., 1986). Such specifically labeled

alcohols are of key importance in studies of lignin biosynthesis and biodegradation.

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